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LETTERS TO THE EDITORS

Moclobemide and the Risk of Serotonin Toxicity (or Serotonin Syndrome)

Comment to the manuscript by Udo Bonnet, Moclobemide: Therapeutic Use and Clinical Studies. *CNS Drug Reviews* 2003;9:97–140.

Recent and important developments in our understanding of serotonin toxicity (ST) or serotonin syndrome (SS) (4,15,23) contribute to an informative re-interpretation of the risk of ST with all drugs, especially with the moclobemide-serotonin reuptake inhibitor (SRI) combinations mentioned in Bonnet's review (1). He suggests "cases of refractory depression might improve with a combination of moclobemide and SSRI." Several such case series of treatment of depression were published, the largest by Hawley (14). In the ensuing years no further papers about the efficacy of such combinations have appeared. Hawley has ceased further exploration of this combination, because of severe ST [see www.psychotropical.com (12)].

Bonnet's statement "this combination has rarely been associated with a potentially lethal serotonin syndrome" is neither precisely formulated nor explained and may be misconstrued. There are a number of reports of *serious* ST with *therapeutic* doses of moclobemide combined with SRIs, some noted by Bonnet, as well as other cases (2,8,18).

Both life-threatening toxicity, and also actual deaths, from "overdoses" of moclobemide as small as 1,050 mg (13) combined with SRIs have occurred (5,6,13,19,21,22). It is noteworthy that in some fatal cases moclobemide blood levels (3–5 mg/L) (15,17) were similar to the peak levels of 2 to 4 mg/L reported by Dingemanse (3) in patients on therapeutic doses of 300–600 mg daily.

A fuller understanding of the seriousness and extent of the danger is facilitated by the spectrum concept of ST. This states that serotonergic drugs produce the reaction of ST, which is a progression from serotonin related side effects at therapeutic doses, through to toxicity in overdose. Not only is there a dose effect relationship from increasing doses of an SRI alone, but also toxicity is greater with the greater elevations of serotonin levels that result from combinations of serotonergic drugs, e.g., MAOIs (including moclobemide) with any SRI (4,7,9,11,16,20,24). ST is not an unpredictable or idiosyncratic reaction like neuroleptic malignant syndrome; it is a predictable form of toxicity. The present slowness to recognize this risk closely parallels the similar slowness to recognize or understand ST caused by the old MAOIs with TCAs (but only those TCAs that are SRIs viz. imipramine and clomipramine): that took at least 20 years. It seems some of us are going to do little better this time round. The details of the history of this sorry story are contained in my 1998 review "Serotonin Syndrome: History and Risk" (9).

The spectrum concept of ST thus provides both a framework for understanding the subject and also makes testable predictions about the frequency and severity of toxicity. The spectrum concept is now strongly supported by the extensive toxico-epidemiological data from the HATS database (4,16,23,24) as well as by animal work reviewed elsewhere (9). The data (16) show that moclobemide very rarely produces severe ST in overdose by itself but frequently does if co-ingested with an SRI. In Whyte's series (4) 11 of 21 cases of co-ingestion of moclobemide with an SRI developed ST and in 6 of these 21 severe ST developed with a temperature >38.5°C and muscle rigidity requiring intubation and paralysis and treatment with 5-HT_{2A} antagonists (cyproheptadine or chlorpromazine).

This brief comment covers and explains but a fraction of the subject of ST and the relative risks with various drugs and combinations. Interested readers may wish to study the much more extensive current analysis "Serotonin toxicity (serotonin syndrome): A current analysis" (10) which is a summary of my three extensive reviews of ST as well as numerous other published comments. It contains a more detailed analysis of the risks with moclobemide, which anyone contemplating combined treatment strategies would be well advised to study.

The above data indicate clearly that such combinations represent a predictably risky strategy. Moclobemide, if combined with any SRI, produces a significant risk of severe ST and also the possibility of fatalities even with "therapeutic" doses. There is no substantive evidence of significant therapeutic benefit. The current medico-legal climate in most western countries means that an informed Doctor, or ethics committee, would be courageous to sanction any such trials except in very special circumstances.

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